

# Cortisol

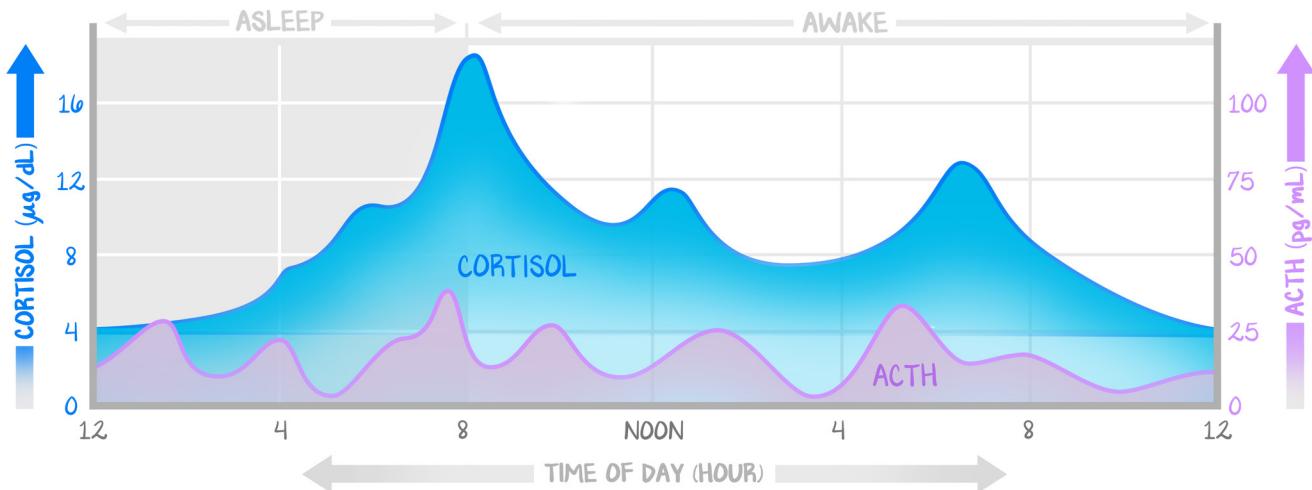
## Introduction

This lesson is dedicated to cortisol. The goal here is to do a deep dive into ACTH and cortisol physiology, use that physiology to review the diagnostic algorithms for too much and too little cortisol, then cover the diseases of cortisol. Because this is endocrinology, we are dealing with hormone pathology, which presents as either excess or deficient hormone effect. And because there are a hypothalamus, anterior pituitary, and adrenal gland, that excess or deficiency could be caused by any of the organs in the axis. Luckily, disorders of cortisol are usually a product of pituitary adenoma (excess cortisol), adrenal adenoma (excess cortisol), or adrenal insufficiency (deficient cortisol).

We'll cover in detail the regulation of the cortisol axis and how ACTH is made and released, then get into the specifics of cortisol function before closing with the diseases of cortisol.

## Deep Dive Into Regulation

CRH (corticotropin-releasing hormone) is released from the hypothalamus into the hypophyseal portal circulation. CRH activates **CRH receptors** on corticotropes. CRH is a water-soluble peptide hormone, so it must act through transmembrane proteins and second messengers. The **CRH receptor** is a G protein-coupled receptor, coupled to a **G<sub>s</sub> protein** that activates the AC-cAMP-PKA pathway. The outcome of this PKA activation is the opening of **L-type Ca<sup>2+</sup> channels**. The influx of calcium enables vesicle fusion and the release of ACTH. The long-term effect of CRH receptor stimulation is to increase the synthesis of the ACTH precursor, discussed later.



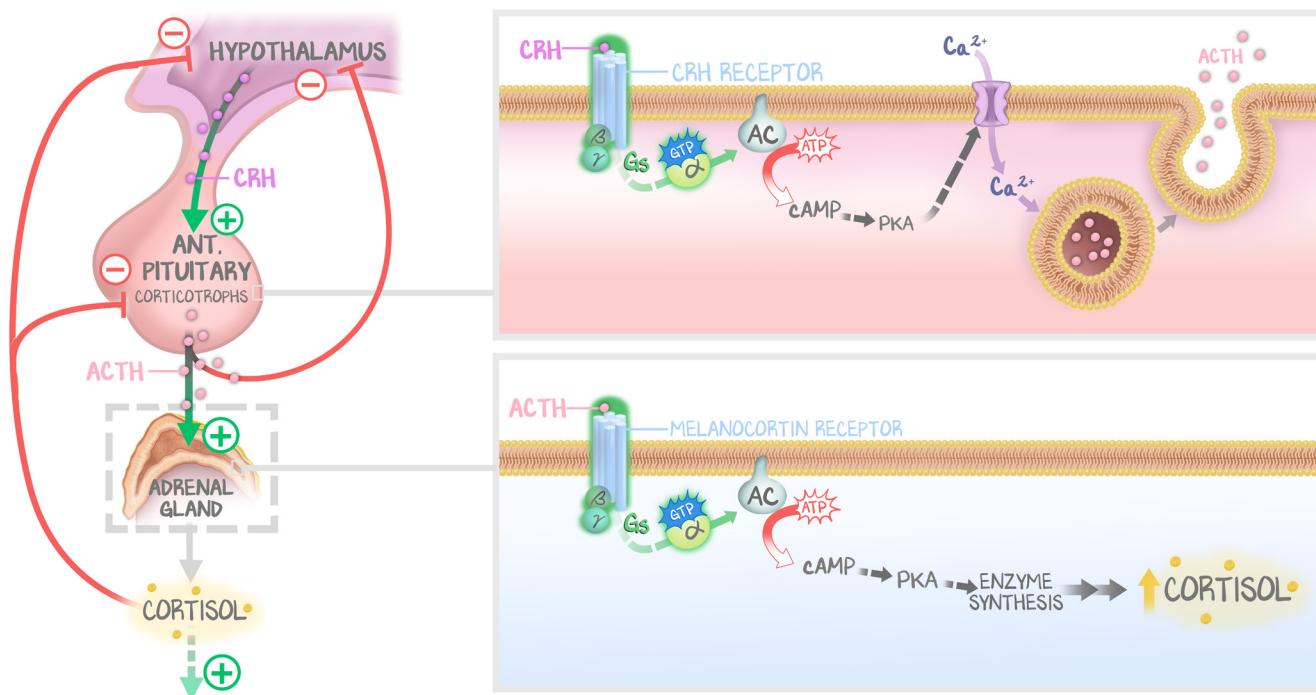
**Figure 2.1: Cortisol Variations**

CRH, ACTH, and cortisol levels vary throughout the day. The hormone with the largest swings is cortisol. Cortisol peaks just prior to when you awaken. Notice there are other, smaller peaks throughout the day, but there are waxing and waning values that are unpredictable. Cortisol will always be highest when you awaken, but through the day, the values cannot be standardized to a normal value. Also, remember that this has nothing to do with the time of day or access to sunlight. Sleeping sets the rhythm.

The release of CRH is affected by **circadian rhythm** as well as **stress**. In this context, stress can be physical (trauma, infection), emotional, or biochemical (hypoglycemia, toxin ingestion). The secretory rates of CRH, ACTH, and cortisol are high in the early morning but low in the late evening. The pulsatile nature of CRH feeds forward ACTH, which feeds forward cortisol. Cortisol peaks occur just after ACTH peaks and cause ACTH levels to fall. In addition to falling cortisol levels disinhibiting

ACTH, the pulsatile nature of CRH sustains large peaks and valleys, as shown in Figure 2.1 (above), the plasma cortisol level ranges between a high of about 20 µg/dL one hour before arising in the morning and a low of about 5 µg/dL around midnight. When a person changes their daily sleeping habits, the cycle changes correspondingly. Therefore, measurements of blood cortisol levels are meaningful only when expressed in terms of the time in the cycle at which the measurements are made. Because the greatest variation occurs in the morning, **early morning cortisol levels should not be used** for random screening.

The release of ACTH from the anterior pituitary results in both the inhibition of CRH release from the hypothalamic neurons and the stimulation of the steroid-secreting cells of the adrenal cortex. ACTH has a receptor on cells in each of the three layers. The name is not ACTH receptor but rather melanocortin-2 receptor (**MC2R**). We'll get to why it has that name in a bit. Like the CRH receptor, the MC2R is a G protein-coupled receptor that acts through  $G_s$ -AC-cAMP-PKA. Because cortisol is a steroid hormone, it cannot be stored in vesicles; thus, there is no mechanism involving sudden calcium influx and vesicle fusion as there is in the anterior pituitary activation of CRH receptors. Instead, ACTH binding to its receptor results in phosphorylation of the enzyme that performs the first step in steroid hormone synthesis, **stimulating the conversion of cholesterol to pregnenolone**. This reaction is also the **rate-limiting step** in cortisol synthesis. Activation through phosphorylation is a rapid effect. In addition, over a longer period, ACTH receptor activation influences gene transcription, upregulating the transcription of all the P450 enzymes required for steroid hormone synthesis and the LDL receptor in order to increase cholesterol uptake. The immediate effect is more cortisol. The delayed effect is an increased ability to make cortisol faster.



**Figure 2.2: Cortisol Release Mechanisms**

CRH is released from the hypothalamus and binds to CRH receptors on corticotropes of the anterior pituitary, activating them. Activated CRH receptors are GPCRs that utilize the  $G_s$ -AC-cAMP-PKA second messenger system. Their activation will eventually lead to the opening of L-type calcium channels and the calcium-induced fusion of pre-made secretory vesicles with ACTH in them. ACTH binds to MC2R, which is also a GPCR that utilizes the  $G_s$ -AC-cAMP-PKA second messenger pathway, on the cells of the adrenal gland. Because cortisol is a lipid-soluble hormone, it cannot be stored in vesicles. Instead, PKA activity (and likely CREB) stimulates the production of steroid hormones by increasing transcription of the enzymes required to make cholesterol hormones. Cortisol has inhibitory effects on the transcription of ACTH in the anterior pituitary and CRH in the hypothalamus.

Cortisol is synthesized and diffuses into the blood. In classic negative feedback, cortisol **inhibits CRH** in the hypothalamus and **inhibits ACTH** release in the anterior pituitary. In the corticotropes of the anterior pituitary, cortisol binds its cytoplasmic receptor, translocates to the nucleus, and **downregulates** the synthesis of both **CRH receptor** and **ACTH**. ACTH is synthesized as a precursor protein (POMC gene, discussed below) and requires post-translational cleavage. Although the POMC gene yields multiple secretory products, cortisol is the sole regulator of POMC gene transcription. The negative feedback of cortisol on the CRH-secreting neurons of the hypothalamus is caused by a reduced CRH transcription rate in paraventricular hypothalamic neurons. The impact on CRH is minor compared to the impact on ACTH. But understand that because cortisol is a steroid hormone, the way it acts on all cells is through modification of transcription.

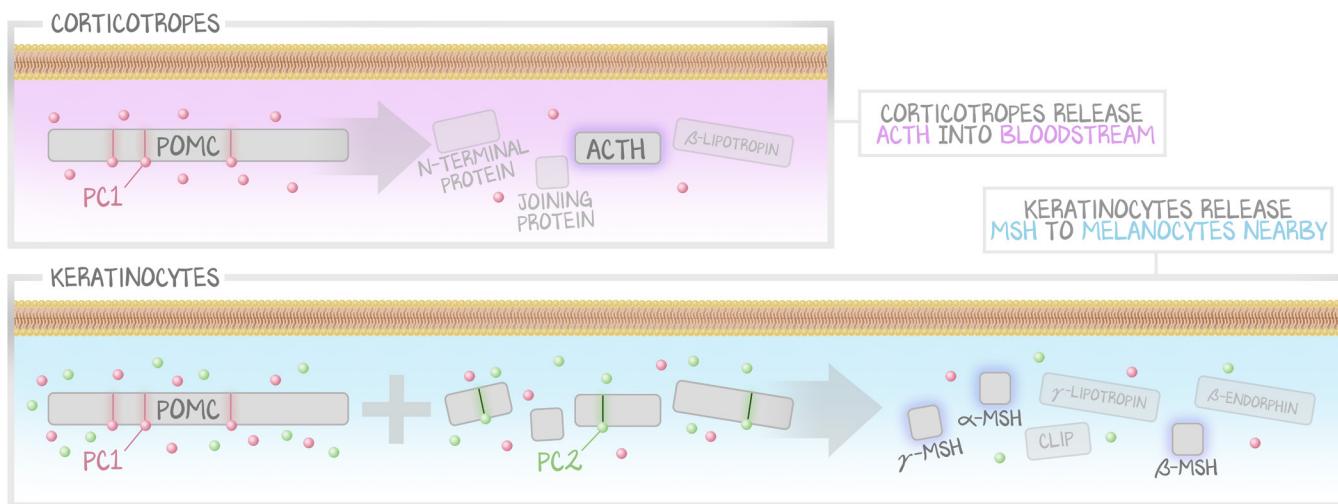
## ACTH Synthesis

Pituitary corticotropes make ACTH through the post-translational cleavage of a large precursor protein called **proopiomelanocortin** (pro-opio-melano-cortin, POMC). The POMC gene codes for the POMC protein. The rate of POMC transcription is tied to both **inhibition** by cortisol via glucocorticoid receptor/glucocorticoid response elements, and **stimulation** via long-term changes from CRH receptor activation and the AC-cAMP-PKA pathway.

The POMC gene is actively transcribed in several tissues, including the corticotropes of the anterior pituitary, POMC neurons in the arcuate nucleus of the hypothalamus, keratinocytes and melanocytes of the epidermis, and lymphoid tissue. In all of these cell types, the large POMC protein is processed to generate several smaller peptides, but different peptides in different tissue. The precise type of POMC-derived products made in a particular tissue depends on the type of processing enzymes present in that tissue. Pituitary corticotropes express prohormone convertase 1 (PC1) but not PC2, resulting in the cleavage of POMC into an N-terminal peptide, a joining peptide, **ACTH**, and  $\beta$ -lipotropin. The expression of both PC1 and PC2 in other cells (brainstem neurons of the analgesia tracts for endorphins; keratinocytes and melanocytes of the skin producing MSH) leads to the production of  $\alpha$ -MSH,  $\beta$ -MSH,  $\gamma$ -MSH, and  $\beta$ -endorphin, but **not ACTH**. The point is that the cells of different tissues will use a common large molecule—POMC—and make the proteins they need by using different PC enzymes. There might be ACTH that hasn't been cleaved yet in a vesicle in a cell. But by the time the molecule it will become is released, all the POMC and ACTH will be gone.

$\beta$ -endorphin is the “opio” portion of POMC, inducing analgesic effects in the CNS (see Neuroscience: Clinical Cortex #7: *Pain and Analgesic Tracts*). Together, ACTH,  $\alpha$ -MSH,  $\beta$ -MSH, and  $\gamma$ -MSH are considered to be the **melanocortins**. You read that correctly. ACTH and the variants of melanocyte-stimulating hormone (MSH) activate **melanocortin receptors**. Melanocortin receptors are all G protein-coupled receptors and are numbered MC1R to MC5R. The MC2R happens to be the receptor on adrenal corticocytes. Although it does have “corti” in the receptor name, the fact that it starts with “melano-“ makes students think it belongs only to melanocytes.

In dermatology, the basal cells appropriately release MSH to melanocytes to induce darkening of the skin in response to sun exposure (Musculoskeletal: Dermatology #5: *Disorders of Skin Pigmentation*). ACTH has the highest affinity for **MC2R**, the melanocyte receptor on the cells of the adrenal cortex. The other MSHs do not have an affinity for MC2R. In return, ACTH has a very low affinity for any other melanocortin receptor, including the melanocortin receptor on melanocytes. However, in conditions of excess ACTH secretion—physiologic response to adrenal failure, an ACTH-secreting pituitary tumor, or small-cell lung cancer—**hyperpigmentation** may result. As the amount of ACTH in the blood increases, despite a low binding affinity for the melanocyte melanocortin receptor, there becomes enough ACTH to activate those melanocyte melanocortin receptors, which induces extra production of melanosomes.



**Figure 2.3: Proopiomelanocortin (POMC)**

Multiple cells utilize the *POMC* gene's POMC protein to make the compounds they need. In all cells, post-translational modification occurs in a membrane-bound organelle, inside which are also proteolytic enzymes. Keratinocytes express the proteolytic enzymes PC1 and PC2. Because they are both active at the same time in the membrane-bound organelle, keratinocytes cannot release ACTH because both PC1 and PC2 are active in the same organelle. Corticotropes cannot make MSH because they lack the enzyme PC2. They can make ACTH because they have PC1. When the vesicle finally fuses, and the hormone is released, all PC enzymes will have done their work. Keratinocytes release MSH; corticotropes release ACTH.

Increased synthesis and release of ACTH by the above-listed pathologies do not cause the anterior pituitary to release MSHs—it lacks the enzymes to do that. And although all reactions can proceed spontaneously, the rate at which an endopeptidase's reaction would occur is super low. Instead, the hyperpigmentation is secondary to enzyme affinity and the relative concentration of ligand.  $\alpha$ -MSH is not a marker used to diagnose or track diseases of excess ACTH. ACTH is.

## Effects of Cortisol

Cortisol, like other steroid hormones, exerts its effects by first interacting with cytoplasmic receptors in target cells. Because cortisol is lipid-soluble, it can easily diffuse through the cell membrane. Once inside the cell, cortisol binds with its **glucocorticoid receptor**, displacing its chaperone protein Hsp90, then translocating to the nucleus. The hormone-receptor complex then interacts with specific regulatory DNA sequences, called **glucocorticoid response elements**, to induce or repress gene transcription. Therefore, most of the metabolic effects of cortisol are not immediate but require 45–60 minutes for proteins to be synthesized and up to several hours or days to fully develop. Cortisol does this in its inhibitory effects on ACTH release and CRH receptor synthesis just as much as it does this in the effects we are about to discuss.

Glucocorticoids are named for their ability to disrupt metabolism. Their effects on metabolism are the same as those of growth hormone. In **hepatocytes**, cortisol transcribes the genes necessary for gluconeogenesis, fatty acid oxidation, and glycogenolysis. In **skeletal muscle**, cortisol stimulates the breakdown of muscle protein, releasing amino acids for uptake by the liver. In **adipocytes**, cortisol induces lipolysis, freeing fatty acids from their triglyceride stored form, releasing those fatty acids back to the liver. Glucocorticoids, growth hormone, glucagon, and epinephrine all have the same effects, each acting through different receptors and each opposing the effects of insulin.

Glucocorticoids do a bunch of other stuff, too. They markedly **decrease eosinophils** and are used as the mainstay for asthma treatment. They also have a profound effect on **fibroblasts**, frankly inhibiting collagen deposition. They inhibit acute inflammation by impairing phagocytosis, reducing lymphocyte replication (lymph nodes get smaller), and inhibiting the arachidonic acid pathway. The further from the metabolic effects we get, the more into anti-inflammatory effects, the less the mechanisms have been elucidated. The thing is, in cortisol excess, what you will be able to identify in patients are the metabolic effects, so those are the ones we focus on.

## Principles of Endocrinology Reviewed

A **primary** endocrine problem is when the gland that makes or releases the effector molecule is defective. The adrenal gland makes cortisol. Any problem with cortisol that is the fault of the adrenal gland is a primary disease. A **secondary** endocrine problem is when the gland that makes or releases the effector molecule is intact but not receiving the appropriate signal from the gland that regulates it. Any problem with ACTH release from the anterior pituitary causing a problem with cortisol is a secondary disease.

In endocrinology, **healthy tissue listens**. In primary cortisol deficiency (the adrenal gland is broken), the pituitary and hypothalamus will be disinhibited, and the signal to make more cortisol will rise. In **primary cortisol deficiency, ACTH will be elevated**. In primary cortisol excess (the adrenal gland is making too much cortisol on its own), the pituitary and hypothalamus will be inhibited, and the signal to make more cortisol will fall. In **primary cortisol excess, ACTH will be low**.

In endocrinology, **cancer does what it wants**. A pituitary adenoma will generate excess ACTH, which in turn generates excess cortisol. The adrenal gland is doing as it is instructed by the ACTH and making excess cortisol. The pituitary adenoma should be inhibited by the excess cortisol. In **secondary hypercortisolism, ACTH is high despite high cortisol**.

In endocrinology, there can be either too much or too little of a hormone. Too much cortisol is called **hypercortisolism**. Hypercortisolism, regardless of the cause, is given the eponym Cushing's syndrome. A syndrome is a constellation of symptoms. The constellation of signs and symptoms of hypercortisolism (Cushing's syndrome) includes **hypertension, diabetes, central obesity** (stretch marks/purple striae, buffalo hump), and **moon facies**. Less frequently seen symptoms are easily bruised skin, osteoporosis, hirsutism (facial hair on women), and mental disturbances. Long-term, hypercortisolism can lead to avascular necrosis of the hip. Too little cortisol is called **hypocortisolism**. The constellation of signs and symptoms of hypocortisolism includes Addison's disease (Addison's for short). Hypocortisolism is characterized by **hypotension, coma, and death** (we'll get to the details in a later section this lesson).

## Working-Up Hypercortisolism

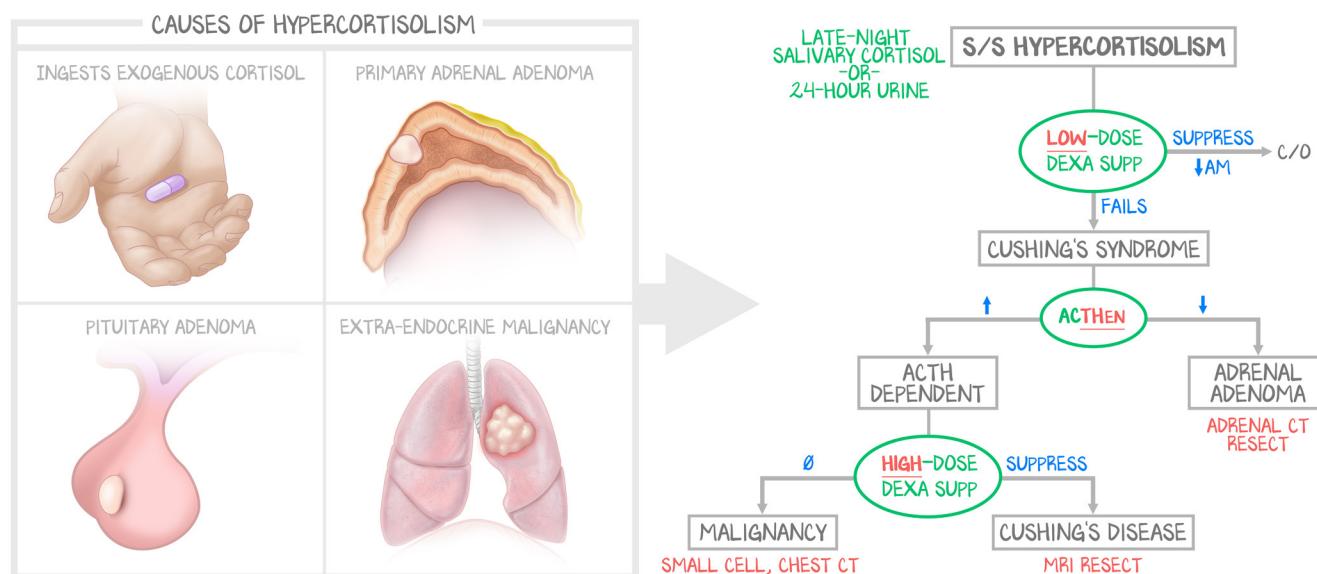
You have a patient whom you believe has excess cortisol. They have hypertension, diabetes, central obesity, acne, purple striae, etc. The first step is to screen them for excess cortisol.

Hypercortisolism comes from one of four causes: production of cortisol by a **primary adrenal tumor**, release of ACTH by a **pituitary adenoma** (causing secondary hypercortisolism), secretion of ACTH by an **extra-endocrine tumor** (like small-cell lung cancer) instead of by the pituitary, or **ingestion of exogenous cortisol**.

The first step is to assess whether they have high cortisol. Cortisol levels peak in the morning and are highly variable, so they should not be used as a screening tool. Two screening tests are appropriate: **24-hour urine cortisol** (inconvenient, requiring the collection of all urine for 24 hours) and **late-night salivary cortisol** (convenient, as it is only one test at one timepoint, but is also the weakest of the tests). If either of these tests is positive, hypercortisolemia (too much cortisol in the blood) is the only diagnosis.

From here, the diagnosis is as simple as “Low Then High”—a **low-dose dexamethasone suppression test** (which serves only to rule out the condition if normal), ACTH<sup>en</sup> (to identify whether the excess cortisol is due to ACTH secretion), a **high-dose dexamethasone suppression test** (to identify whether the secretion is from a pituitary lesion or an extra-endocrine one). ACTH-independent hypercortisolism (one with low ACTH) is caused by exogenous use and adrenal adenoma. ACTH-dependent hypercortisolism (one with high ACTH) is either from a pituitary adenoma secreting ACTH or an extra-endocrine malignancy producing ACTH as a paraneoplastic syndrome (small-cell lung cancer). The high-dose dexamethasone suppression test is only needed to separate the pituitary adenoma from the small-cell lung cancer, and that points you to which imaging modality and where to point the lens—if it suppresses, look in the brain; if it doesn’t, look in the chest.

Being able to follow this algorithm, interpret the results, or choose the next step is most appropriate for clinical sciences; in other words, not skills you need yet. Instead, because we are starting at the diagnosis and then predicting the labs, after each diagnosis, you should come back here and work through the labs and imaging in this algorithm to arrive at the diagnosis.

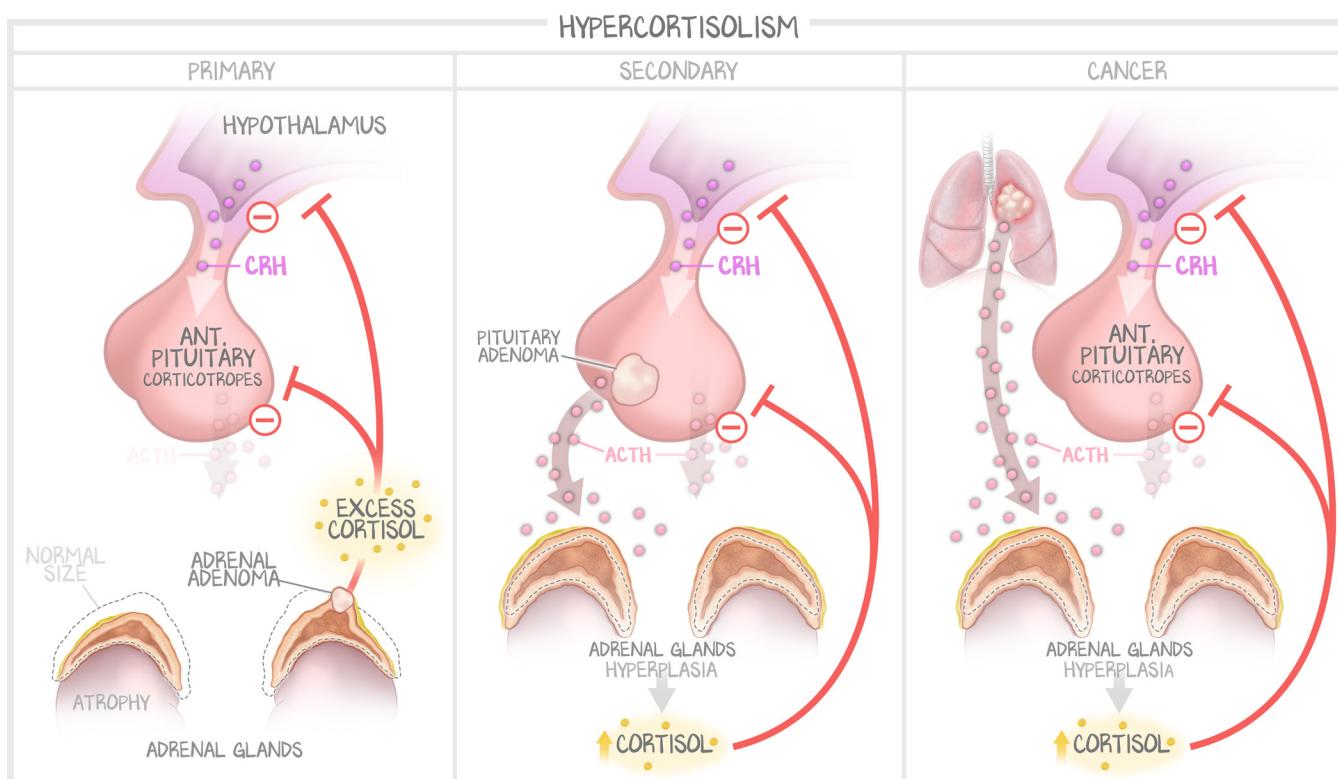


**Figure 2.4: Work-up for Hypercortisolism**

Once you learn the pathogenesis of each of the causes of hypercortisolism, use the expected values to trace your way to the diagnosis using this flow chart.

**Primary hypercortisolism.** The **adrenal gland** develops a tumor that hypersecretes cortisol. The cortisol is elevated because the tumor does whatever it wants, producing cortisol without the feedforward signal from the hypothalamus. **Cortisol is elevated.** A low-dose dexamethasone suppression test suppresses cortisol levels by acting as exogenous cortisol, inhibiting the production of ACTH and thereby inhibiting the production of cortisol. It only suppresses when there isn't a problem with excess cortisol. So, the **low-dose dexamethasone test will fail to suppress it.** Every other tissue is assumed to be acting normally. Cortisol inhibits CRH and **inhibits ACTH.** Because there is excess cortisol, serum levels of **ACTH will be low.** As there is no cortisol-secreting tumor known to medical science other than the one that occurs in the adrenal gland, with the ACTH low and the cortisol high, the problem must be arising in one of the adrenal glands. **CT or MRI** of the abdomen will reveal the diagnosis. Because cancers tend to originate from one cell, only **one adrenal gland** will be hypertrophied—the one with the tumor secreting cortisol. Because ACTH is low, the **other adrenal gland will be atrophied.** Without the ACTH signal to sustain it, the healthy adrenal gland atrophies.

**Secondary hypercortisolism.** The adrenal gland is normal. The anterior pituitary develops a tumor that hypersecretes ACTH. The ACTH is elevated because the tumor does whatever it wants, producing ACTH and ignoring all endocrine signals (the excess cortisol doesn't inhibit the tumor cells). Because ACTH is elevated, **cortisol is elevated**. Cortisol inhibits CRH and is supposed to inhibit the anterior pituitary. It doesn't matter, though, because the pituitary tumor won't listen. The **low-dose dexamethasone suppression test will fail to suppress** because there is disease. The cortisol is elevated because **ACTH** is high. But this tumor is within an endocrine gland. That means if the signal is loud enough, the tissue will still be able to hear it. A **high-dose dexamethasone suppression test will succeed in suppressing** the cortisol levels. That's what the high dose is for. If it suppresses, there is a tumor, and that tumor is in the brain, so MRI will find it. If imaging of the abdomen were performed (which isn't necessary and shouldn't be done), **both adrenals would show hypertrophy**. The ACTH stimulus is delivered to both, and the excess ACTH leads to excess proliferation as well as the excess release of cortisol.



**Figure 2.5: Hypercortisolism**

A visual explanation of how cortisol levels are what they are based on the organ that is autonomously secreting and what it is secreting—either ACTH or cortisol. In primary hypercortisolism, there is excess cortisol from an adrenal adenoma. ACTH levels are silenced, so the remaining adrenal glands atrophy. In secondary hypercortisolism, excess ACTH is produced by the pituitary, causing bilateral hypertrophy and excess cortisol. In the paraneoplastic syndrome of squamous cell lung cancer, the same effect is seen as in pituitary adenoma, except the pituitary is silenced.

**Small-cell lung cancer.** The adrenal gland is normal. The anterior pituitary is normal. The **lung** develops cancer that secretes ACTH (this is just one paraneoplastic syndrome of small-cell lung cancer, but it is the only one we care about here). ACTH is elevated because the tumor does whatever it wants, and because it is **an extra-endocrine tumor**, it won't listen to any signal. Because ACTH is elevated, cortisol is elevated. Cortisol inhibits CRH and ACTH—**anterior pituitary ACTH will be low**. But it doesn't matter that the anterior pituitary is responding appropriately: the lung cancer is making ACTH anyway. The low-dose dexamethasone suppression test will fail to suppress, ACTH is high because of the cancer, and a **high-dose dexamethasone suppression test will fail to suppress** because lung cancer can't listen to the endocrine

signal no matter how loud. If imaging of the abdomen were performed (which shouldn't be done because it isn't necessary), **both adrenals** would show **hypertrophy**. The ACTH stimulus is delivered to both, and the excess ACTH leads to excess proliferation as well as the excess release of cortisol (the same as in the pituitary ACTH tumor).

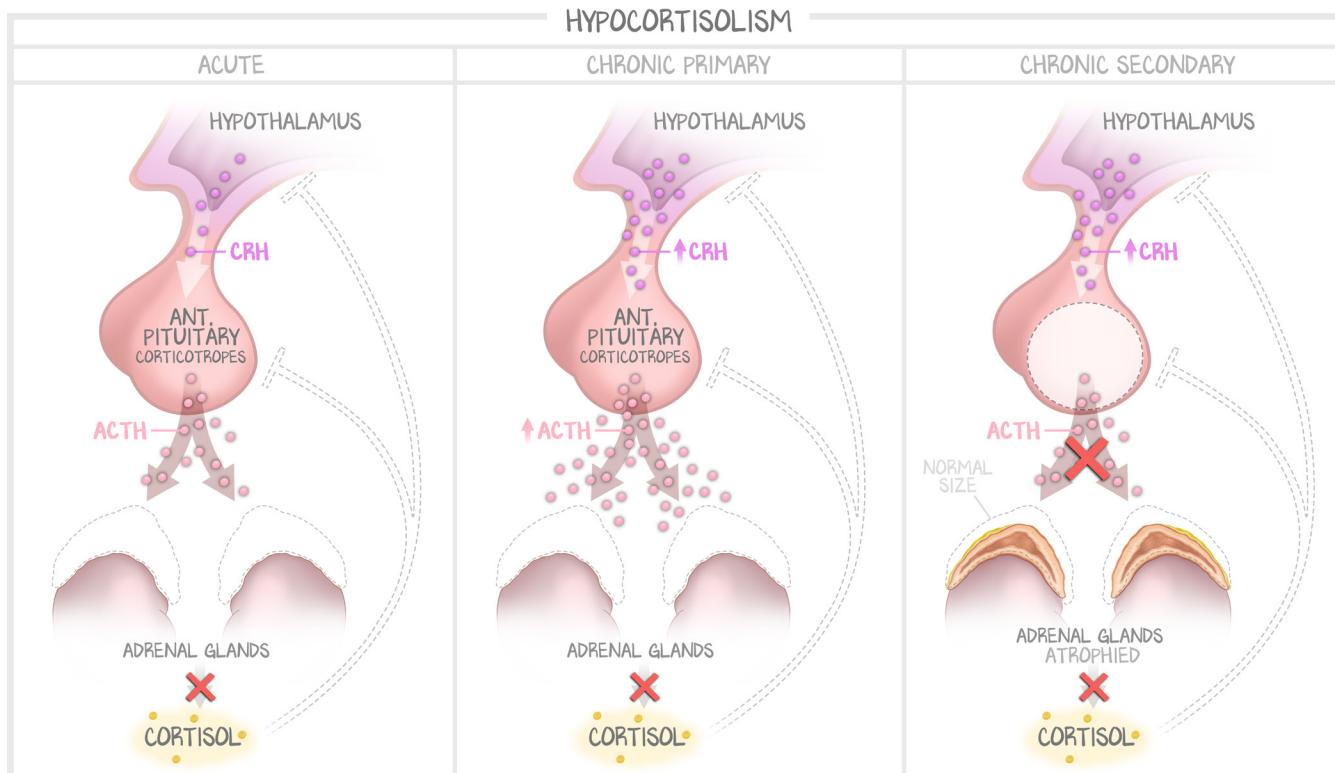
**Exogenous administration.** The adrenal gland is normal. The anterior pituitary is normal. If a patient is taking steroids for a diagnosis, their med list will show you that, and this work-up need not be pursued. But when it is a diagnostic mystery (the patient is ingesting intentionally and not informing you of that ingestion), intentional exogenous administration to induce symptoms that warrant an investigation is likely to be fictitious or malingering disorder. The cortisol is elevated because the patient is intentionally ingesting cortisol. A low-dose dexamethasone suppression will fail to suppress because the conscious human, not the hypothalamus or pituitary gland, controls the cortisol release. Cortisol inhibits CRH and ACTH, which will be low. A high-dose dexamethasone suppression test fails to suppress as well, because the patient continues to ingest cortisol, and there is no gland to suppress. The entire body is imaged, and no lesion is found. BUT . . . abdominal imaging is likely to find something else. Because the person has been suppressing both endogenous ACTH and cortisol production, there will be **atrophy of the adrenal glands**. It would be better to find out that they are lying before doing any of these tests, and there is no need to perform these tests for a person who requires steroids as medical treatment, but it was a meaningful exercise to walk you through the thought processes.

## Hypocortisolism

Low levels of cortisol is called hypocortisolism, adrenal insufficiency, adrenocortical insufficiency, or hypoadrenalinism. These terms are used interchangeably, as they are synonyms, but rarely does the same author use more than one. Because conditions that affect the adrenal cortex directly affect the entire cortex and not just the cortisol-producing cells, there will be effects of deficient cortisol and aldosterone. Therefore, when a lesion is **primary**, we choose to say **primary adrenocortical insufficiency**, implying that more than just cortisol is compromised. For conditions that affect the pituitary release of ACTH, which will affect mostly the cortisol-secreting cells of the reticularis (and a little fasciculata), but will spare the angiotensin-2-stimulated zona glomerulosa's production of aldosterone, we choose to say **secondary hypocortisolism**, implying in the name that only cortisol is deficient.

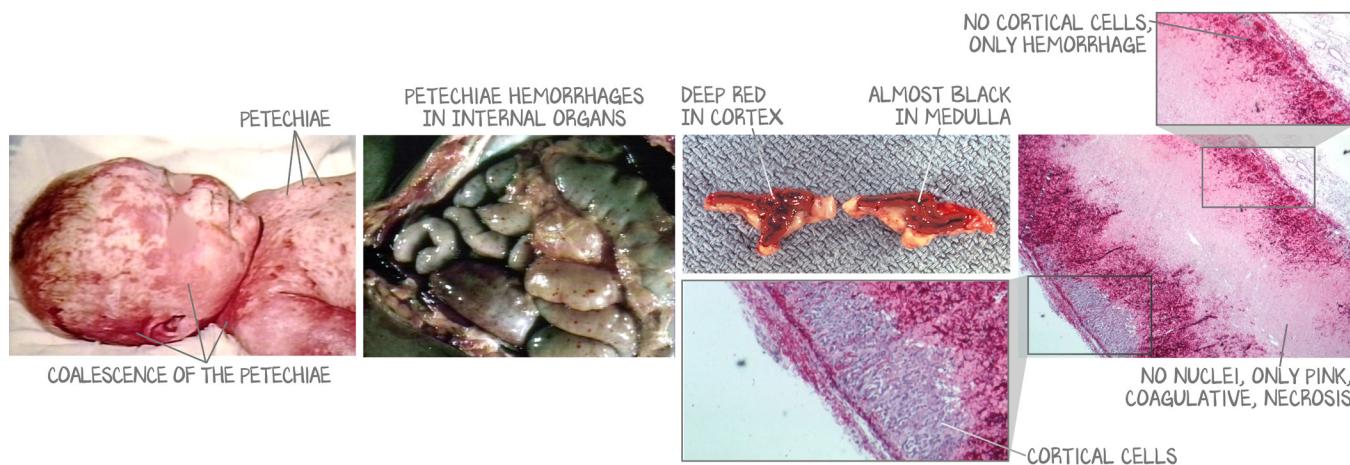
Theoretically, a lesion of the hypothalamus could cause secondary hypercortisolism. Theoretically, a defect in any of the receptors along the axis could also cause hypocortisolism. Fortunately, there only three patterns of hypocortisolism you need to be aware of: (1) primary **acute adrenocortical insufficiency** (also called **adrenal crisis**), (2) primary **chronic adrenocortical insufficiency** (also called Addison's disease), and (3) **secondary hypercortisolism** from a pituitary lesion.

Chronic adrenal insufficiency can be assessed with a **cosyntropin stimulation test**. Cortisol levels are assessed at timepoint 0. A fixed dose of cosyntropin (ACTH) is administered intravenously. The values of cortisol are obtained at 30, 60, and 90 minutes. If there is **no rise in cortisol**, then it is the adrenals that cannot respond to the signal. If there is **a rise in cortisol**, the pituitary has not been sending sufficient signal to the adrenal glands

**Figure 2.6: Hypocortisolism**

In acute hypocortisolism, there is a sudden loss of cortisol from a sudden loss of the adrenal glands, without time for the anterior pituitary to compensate, so ACTH levels are normal. In chronic primary hypocortisolism, there is a gradual loss of cortisol from a gradual loss of the adrenal glands, with a compensatory rise in ACTH. In chronic secondary hypocortisolism, normal adrenal glands atrophy because of the loss of ACTH.

**Acute primary adrenocortical insufficiency.** Very rarely does a patient present with normal adrenal glands and then precipitously lose both. The condition in which it does happen is a result of **massive adrenal hemorrhage**. This can occur in newborns following a prolonged and difficult delivery with trauma and hypoxemia, patients with coagulopathy in general, or patients who develop **disseminated intravascular coagulation** (DIC). When that DIC and adrenocortical insufficiency are caused by an overwhelming bacterial infection, it is called **Waterhouse-Friderichsen syndrome**. Classically associated with *Neisseria meningitidis* infections that present with overwhelming sepsis, the combination of septic shock and DIC results in bilateral adrenal hemorrhage.

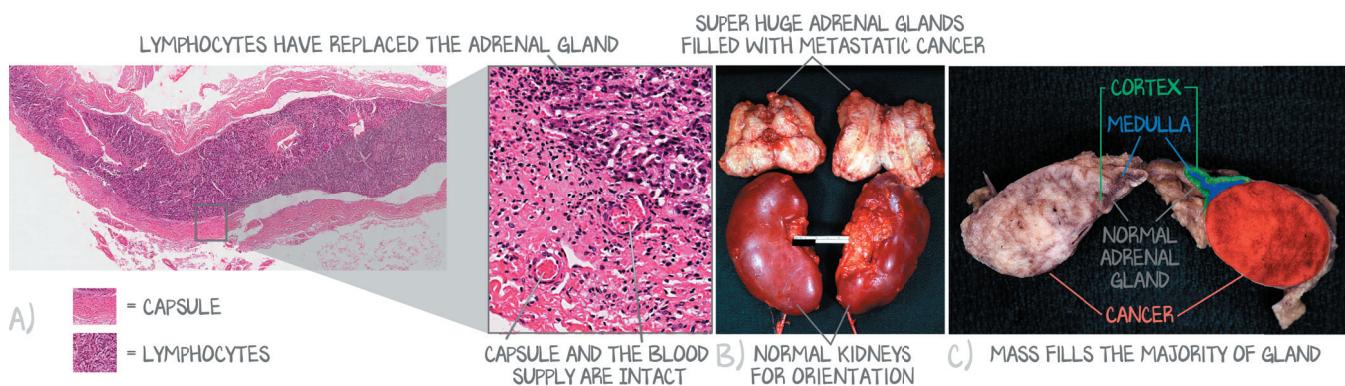
**Figure 2.7: Waterhouse-Friderichsen Syndrome**

(a) Within 1 day of symptom onset, this child succumbed to *Neisseria*-associated meningitis, which caused disseminated intravascular coagulation (DIC). The petechiae on his chest are visible as discrete macules. On his face, ear, and shoulder, they have coalesced into large patches. They are a sign of thrombocytopenia and, thus, DIC. They do not represent disseminated bacteria (though bacteremia was also found in this case). (b) On autopsy, multiple petechial hemorrhages were found throughout all organs. They also represent thrombocytopenia and an increased risk of bleeding. Petechial hemorrhages on visceral organs will almost always be seen only on autopsy, as surgery would be far too risky. (c) The adrenal glands are highly vascular, and, as petechiae are a sign of thrombocytopenia and increased risk of bleeding, they are the organ at the highest risk for frank hemorrhage. These adrenal glands are small (because they belong to a young child) and filled with blood. (d) A low-powered view of the adrenal gland identifies areas of hemorrhage in the cortex (the red stuff) and frank necrosis of the medulla (the pink stuff has no blue dots in it). There is an area of viable cortex, but due to the loss of cortex and medulla in most of the gland, this patient died.

Instead, relative acute primary adrenocortical insufficiency is more likely to occur in someone who already has a problem with their adrenal glands. Cortisol rises acutely when a person is stressed. If a person has required the use of chronic systemic steroids, their **adrenals atrophy**. The oral corticosteroids are titrated to achieve their intended effect. But that means the dose the person takes is fixed, and the adrenal glands, being atrophied, cannot respond to increases in CRH or ACTH under periods of intense stress. Thus, a **relative adrenal crisis** may occur when a person on chronic systemic steroids becomes stressed and requires more steroids, but, unaware of the increased needs, does not adjust the dose accordingly. Simply providing more steroids acutely can get a patient out of that sort of adrenal crisis. The other way an acute crisis occurs is if a patient who has an atrophied adrenal gland because of chronic exogenous administration of cortisol (the exogenous cortisol resulting in bilateral adrenal gland atrophy) has the source of exogenous cortisol **abruptly withdrawn**. This is why oral steroids require a taper if used for more than 2 weeks. The exogenous administration inhibited both the ACTH-secreting cells of the pituitary and the corticotropes of the adrenal gland. The slowly decreasing dose of a taper allows ACTH to come back online and the atrophic adrenal glands to pick back up. This is also why patients who have surgical removal of a primary adrenal tumor secreting cortisol are placed on oral steroids—with the cancer gone, the normal adrenal gland needs time to wake back up. Patients with acute primary adrenocortical insufficiency have not had enough time to generate the ACTH levels necessary to cause hyperpigmentation.

**Chronic primary adrenocortical insufficiency.** Chronic (means insidious and slow onset, as both acute and chronic are permanent) adrenocortical insufficiency is a slow-onset, progressive destruction of the adrenal cortex. Only after 90% of the cortex is gone do people start feeling symptoms. The leading cause worldwide is **tuberculosis**; the leading cause in the US is autoimmune disease (**autoimmune adrenalitis** tends to form antibodies against the CYP450 enzymes that synthesize steroid hormone, such as 21 $\alpha$ -hydroxylase or 17 $\alpha$ -hydroxylase, thus claiming the cortex and sparing the medulla).

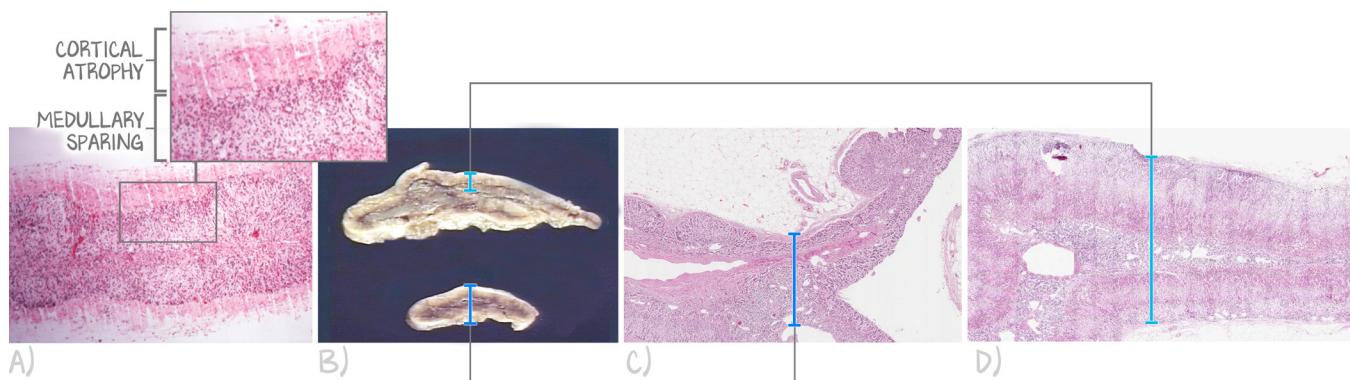
The other causes include AIDS-related complications and **metastatic tumors to the adrenals** (most common are breast and lung carcinomas). The problem here is a deficiency of both mineralocorticoids and glucocorticoids. Initially, nonspecific symptoms, such as progressive weakness, easy fatigability, and gastrointestinal complaints, predominate. Because cortisol is low, the feedback inhibition on ACTH release is low. With the absent cortisol inhibition of the *POMC* gene, excess *POMC* transcription occurs, driving the **ACTH level very high**. This increase in ACTH generates a high enough concentration to bind and activate the **MC1R** melanocyte receptor, leading to **skin hyperpigmentation**. Additionally, because of a deficiency of aldosterone, sodium is not reabsorbed from the collecting duct. This leads to **volume depletion** but not a change in osmolarity, as ADH is still intact. The electrolyte effect is from the failure to reabsorb sodium at the cost of potassium. Hyperkalemia is another stimulator of aldosterone, but without the cells to make it, **hyperkalemia** develops. Volume depletion leads to **hypotension**. From deficient cortisol, there are confusion, coma, and more hypotension. Death will result if not started on the hormones they need—**both prednisone** (or any other oral glucocorticoid) and **fludrocortisone** (aldosterone agent) are required.



**Figure 2.8: Chronic Primary Hypocortisolism**

(a) Very low-magnification adrenal gland section demonstrating how very much unlike an adrenal gland it looks and providing context for the inset, in which the capsule is intact, but there is no evidence of cortical cells, the entire gland having been invaded by lymphocytes. This is autoimmune adrenalitis, the most common cause of primary hypocortisolism in the United States. (b) Two extremely large adrenal glands sit atop normal kidneys, used for relative size comparison. The adrenal glands are uncut, seen from the outside. Within, massive amounts of metastatic cancer are waiting for the pathologist. (c) A different set of adrenal glands than in panel b. These glands have been cut open, their other half removed. The right side has been colorized to help you distinguish structures in their natural colors on the contralateral side.

**Secondary hypocortisolism.** When it is a defect of the anterior pituitary that causes low cortisol levels, the symptoms are isolated to the effects of cortisol and not those of aldosterone. Therefore, the volume depletion and electrolyte disturbances will not be present. Likewise, because there is not excessive ACTH being made (the defect is that too little is being made), there is no excess concentration to stimulate melanocytes, and there is **no skin hyperpigmentation** and **no hyperkalemia**. The adrenal glands themselves are normal, but without a trophic signal from ACTH, the glands **atrophy**. The more common cause of secondary adrenal insufficiency is the use of oral steroids. Silencing the ACTH signal also causes the adrenal glands to atrophy. This is what provokes the acute relative adrenal crisis above.



**Figure 2.9: Chronic Secondary Hypocortisolism**

(a) Adrenal gland of a patient who underwent a pituitary resection for ocular disturbances due to a pituitary adenoma. Because all trophic signals were lost, he was placed on thyroid hormone replacement and fludrocortisone (aldosterone) and prednisone (cortisol) replacement therapies. The adrenal gland is fully functional but has become so atrophied that there appears to be hardly any cortical cells. The medulla is preserved as it functions independently of any pituitary axis.  
(b) Comparison of a normal-sized adrenal gland to an extremely atrophic one (below). The size corresponds to the relative thickness of the cortex, as seen in the atrophic gland (c) and the normal gland (d).